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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
| 09/674,183 | 11/14/2000 | Rino Rappuoli | PP00362.102 | 3087 |
| 27476 | 7590 | 04/26/2004 | EXAMINER | |
| Chiron Corporation Intellectual Property - R440 P.O. Box 8097 Emeryville, CA 94662-8097 | | | DEVI, SARVAMANGALA J N | |
| | | | ART UNIT | PAPER NUMBER |
| | | | 1645 | |

DATE MAILED: 04/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | |
|------------------------------|-----------------|----------------|
| Office Action Summary | Application No. | Applicant(s) |
| | 09/674,183 | RAPPOLI ET AL. |
| | Examiner | Art Unit |
| | S. Devi, Ph.D. | 1645 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 06 February 2004.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 4-6,8,10-16,21 and 33-44 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 4-6,8,10-16,21 and 33-44 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

| | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date: _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date: _____ | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| | 6) <input type="checkbox"/> Other: _____ |

RESPONSE TO APPLICANTS' AMENDMENT

Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 11/07/03 and 02/06/04 in response to the non-final Office Action mailed 08/01/03. With this, Applicants have amended the specification.

Status of Claims

2) Claims 4-6, 8, 10, 11, 13-16 and 21 have been amended via the amendment filed 02/06/04.
Claims 1-3, 7, 9, 17-20 and 22-32 have been canceled via the amendment filed 02/06/04.
New claims 33-44 have been added via the amendment filed 02/06/04.
Claims 4-6, 8, 10-16, 21 and 33-44 are pending and under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

5) The objection to the specification made in paragraph 9(a) of the Office Action mailed 08/01/03 is withdrawn in light of Applicants' amendment to the specification.

6) The objection to the specification made in paragraph 9(b) of the Office Action mailed 08/01/03 is withdrawn in light of Applicants' amendment to the specification.

7) The objection to the specification made in paragraph 9(c) of the Office Action mailed 08/01/03 is withdrawn in light of Applicants' amendment to the specification.

8) The objection to the drawings made in paragraph 7 of the Office Action mailed 08/01/03 is withdrawn in light of Applicants' submission of formal drawings.

Rejection(s) Moot

9) The rejection of claims 1 and 2 made in paragraph 10(a) of the Office Action mailed 08/01/03 under 35 U.S.C § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claims.

10) The rejection of claims 2, 3, 7, 9 and 17 made in paragraph 10(b) of the Office Action mailed 08/01/03 under 35 U.S.C § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claims.

11) The rejection of claims 2, 3 and 7 made in paragraph 10(c) of the Office Action mailed 08/01/03

under 35 U.S.C § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claims.

12) The rejection of claim 7 made in paragraph 10(d) of the Office Action mailed 08/01/03 under 35 U.S.C § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claim.

13) The rejection of claims 2, 3, 7, 9, 17, 19 and 23 made in paragraph 10(i) of the Office Action mailed 08/01/03 under 35 U.S.C § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claims.

14) The rejection of claims 1-3, 17, 19 and 23 made in paragraph 12 of the Office Action mailed 08/01/03 under 35 U.S.C § 102(b) as being anticipated by Peeters *et al.* (*Infect. Immun.* 60: 1826-1833, 1992) as evidenced by Falugi *et al.* (*Eur. J. Immunol.* 31: 3816-3824, 2001), is moot in light of Applicants' cancellation of the claims.

15) The rejection of claims 1-3, 17 and 19 made in paragraph 13 of the Office Action mailed 08/01/03 under 35 U.S.C § 102(b) as being anticipated by Jennings *et al.* (*In: Seminars in Infectious Disease.* (Ed) Weinstein *et al.* Volume IV, Chapter 34, 247-253, 1982) as evidenced by Falugi *et al.* (*Eur. J. Immunol.* 31: 3816-3824, 2001), is moot in light of Applicants' cancellation of the claims.

16) The rejection of claims 1 and 7 made in paragraph 14 of the Office Action mailed 08/01/03 under 35 U.S.C § 102(b) as being anticipated by Nussenzweig *et al.* (WO 86/05790) as evidenced by Falugi *et al.* (*Eur. J. Immunol.* 31: 3816-3824, 2001), is moot in light of Applicants' cancellation of the claims.

Rejection(s) Withdrawn

17) The rejection of claim 13 made in paragraph 10(a) of the Office Action mailed 08/01/03 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

18) The rejection of claims 4-6 and 8 made in paragraph 10(c) of the Office Action mailed 08/01/03 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

19) The rejection of claim 11 made in paragraph 10(e) of the Office Action mailed 08/01/03 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

20) The rejection of claims 14 and 15 made in paragraph 10(f) of the Office Action mailed 08/01/03 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

21) The rejection of claim 16 made in paragraph 10(g) of the Office Action mailed 08/01/03 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the

claim.

22) The rejection of claim 21 made in paragraph 10(h) of the Office Action mailed 08/01/03 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

23) The rejection of claims 4, 8, 10-12, 14, 16 and 21 made in paragraph 12 of the Office Action mailed 08/01/03 under 35 U.S.C § 102(b) as being anticipated by Peeters *et al.* (*Infect. Immun.* 60: 1826-1833, 1992) as evidenced by Falugi *et al.* (*Eur. J. Immunol.* 31: 3816-3824, 2001), is withdrawn in light of Applicants' amendments to the claims and/or the base claim(s).

24) The rejection of claims 4, 8, 10, 11, 13-16 and 21 made in paragraph 13 of the Office Action mailed 08/01/03 under 35 U.S.C § 102(b) as being anticipated by Jennings *et al.* (*In: Seminars in Infectious Disease.* (Ed) Weinstein *et al.* Volume IV, Chapter 34, 247-253, 1982) as evidenced by Falugi *et al.* (*Eur. J. Immunol.* 31: 3816-3824, 2001), is withdrawn in light of Applicants' amendments to the claims and/or the base claim(s).

Rejection(s) Maintained

25) The rejection of claims 4-6, 8 and 10-16 made in paragraph 10(b) of the Office Action mailed 08/01/03 under 35 U.S.C § 112, second paragraph, as being indefinite, is maintained for reasons set forth therein.

26) The rejection of claims 4-6 made in paragraph 10(d) of the Office Action mailed 08/01/03 under 35 U.S.C § 112, second paragraph, as being indefinite, is maintained for reasons set forth therein.

Applicants point to Table I on page 36 and state that HA and MT epitopes are defined, and therefore the claims are sufficiently clear.

Applicants' argument has been carefully considered, but is not persuasive. Table I does not provide the description as to what HA, MT and other abbreviations stand for. Without the full terminology, it is unclear whether 'MT' stands for '*Mycobacterium tuberculosis*', or 'HA' stands for hyaluronic acid etc. Therefore, the rejection stands.

27) The rejection of claims 4-6, 8 and 21 made in paragraph 10(i) of the Office Action mailed 08/01/03 under 35 U.S.C § 112, second paragraph, as being indefinite, is maintained for reasons set forth therein.

New Rejection(s)

Applicants are asked to note the new rejection(s) made in this Office Action. Applicants' amendments and submission of new claims, necessitated the new ground(s) of rejection presented in this Office Action.

Rejection(s) under 35 U.S.C. § 112, First Paragraph

28) Claim 4 and those that depend therefrom are rejected under 35 U.S.C § 112, first paragraph, as

containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The amended claim 4 now includes the limitations: ‘further wherein at least one of said CD4+ T cell epitopes is a HBVnc, HA, HbsAg, MT or hsp70 CD4+ T cell epitope’. Applicants do not point to specific parts of the specification that provides support for the added limitations. A review of the specification indicates that the specification, as originally filed, is supportive of a carrier protein genus (for example, the original claim 1-3) and of specific carrier protein species (for example, the original claims 5-7). However, the specific subgenus carrier protein now claimed in claim 4 has no descriptive support in the specification, as originally filed. Therefore, the above-identified new limitations in claim 4 are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support in the specification as filed, for the newly added limitation(s), or to remove the new matter from the claim(s).

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

29) Claims 33-40, 43 and 44 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claims 33-40 lack proper antecedent basis in the limitation: ‘A carrier protein according to claim ...’ as opposed to --The carrier protein according to claim ...--...

(b) Claims 43 and 44, which depend directly or indirectly from claim 39 or 40, are also rejected as being indefinite because of the indefiniteness or vagueness identified above in the base claim.

Rejection(s) under 35 U.S.C. § 102

30) Claims 4, 8, 10 and 21 are rejected under 35 U.S.C. § 102(b) as being anticipated by Brown *et al.* (EP 0 270 295 A2) as evidenced by Falugi *et al.* (*Eur. J. Immunol.* 31: 3816-3824, 2001 – already of record).

It is noted that the transitional recitation “comprising” is open-ended claim language and therefore does not exclude additional unrecited elements. See MPEP 2111.03 [R-1].

Brown *et al.* taught an immunogenic protein vaccine composition comprising a normally weakly immunogenic viral protein, such as, influenza viral haemagglutinin (i.e., HA) covalently bonded to a strongly immunogenic protein, such as, tetanus toxoid (see claims 1-5). The prior art protein contains epitopes that elicit specific T-cell proliferation (see page 2). That the prior art HA-TT protein contains at least five human CD4+ T cell epitopes i.e., P23TT, P32TT, P21TT, P30TT and P2TT, and is made up of oligomeric peptides

is inherent from the teachings of Brown *et al.* in light of what is well known in the art. For instance, Falugi *et al.* showed that TT contains at least five CD4+ T cell epitopes in TT, i.e., P23TT, P32TT, P21TT, P30TT and P2TT (see Table 1 of Falugi *et al.*).

The teachings of Brown *et al.* anticipate the instant claims. Falugi *et al.* is **not** used as a secondary reference in combination with Brown *et al.*, but rather is used to show that every element of the claimed subject matter is disclosed by Brown *et al.* with the unrecited limitation(s) being inherent in view of what is known in the art as explained above. See *In re Samour* 197 USPQ 1 (CCPA 1978).

Claims 4, 8, 10 and 21 are anticipated by Brown *et al.*

Rejection(s) under 35 U.S.C. § 103

31) The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness.

32) Claims 4 and 11-16 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Jennings *et al.* (*In: Seminars in Infectious Disease*. (Ed) Weinstein *et al.* Volume IV, Chapter 34, 247-253, 1982) or Lees (US 5,651,971) as evidenced by Falugi *et al.* (*Eur. J. Immunol.* 31: 3816-3824, 2001) in view of Brown *et al.* (EP 0 270 295 A2) and Classen *et al.* (US 5,728,385 A2).

The teachings of Brown *et al.* are disclosed above, which do not teach their TT-HA protein being conjugated to a polysaccharide.

However, Jennings *et al.* taught covalently linking or conjugating a polysaccharide of *N. meningitidis* to the protein carrier, TT, by reductive amination to produce a vaccine. One conjugate contained 2 protein units per polysaccharide (see abstract; Table 1; and pages 248-250).

Lees disclosed a conjugate wherein the polysaccharide of *Haemophilus influenzae* type B is covalently linked to tetanus toxoid (see last full paragraph in column 10).

Classen *et al.* taught the practice in the art of adding a non-pediatric immunogen from influenza virus

to a pharmaceutical preparation comprising pediatric immunogens, such as, tetanus immunogen and conjugated bacterial polysaccharide immunogen such as that of *Haemophilus influenzae* (see second full paragraph in column 26; and claims 1, 5 and 6).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use Brown's HA-TT protein in place of Jennings' or Lees' TT protein to produce the instant invention with a reasonable expectation of success. Given the disclosure of Classen *et al.* that an influenza immunogen is conventionally added to a pediatric immunogen composition comprising tetanus and conjugated *H. influenzae* immunogens, one of ordinary skill in the art would have been motivated to produce the instant invention for the expected economical benefit of providing both the pediatric TT immunogen and the non-pediatric influenza HA immunogen in a single molecule in order to produce, advantageously, a multivalent or combination vaccine.

Claims 4 and 11-16 are *prima facie* obvious over the prior art of record.

Remarks

33) Claims 4-6, 8, 10-16, 21 and 33-44 stand rejected.
34) Applicants' amendments necessitated the new ground(s) of rejection presented in this Office action.

THIS ACTION IS MADE FINAL. Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

35) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center which receives transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.
36) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette

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Smith, can be reached at (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

April, 2004



S. DEVI, PH.D.
PRIMARY EXAMINER